

SAS/AC:gtc 03/18/04 263459  
PATENTAttorney Reference Number 4239-58378  
Application Number 09/807,148**Remarks**

Claims 1-8, 13-17, 20-25, 57, 60-70, and 77-81 are pending. Claims 2-4, 7, 8, 61, 65, and 67 are withdrawn from consideration. Claims 1 and 5 are amended herein. Claim 1 is amended to incorporate the limitations of canceled claim 62. Claim 5 is amended to incorporate the limitations of canceled claim 68. Support for additional amendments of claims 1 and 5 can be found in the specification at page 2, lines 6-14, page 3, lines 3-6, page 11, lines 5-28, page 12, lines 26-39 and page 38, lines 23-32.

Claims 62 and 68 are canceled herein. Claims 9, 12, 18-19, 25-56, 58-59 and 71-76 were canceled previously. Following entry of this amendment, claims 1, 5, 6, 13-17, 20-25, 57, 60, 63-64, 66, 69-70, 77-81 are pending.

No new matter is added herein. Reconsideration of the subject application is respectfully requested.

**Telephone interview**

Applicants thank Examiners Yu and Helms for the helpful telephone conference on February 24, 2004, with Applicant's representatives, Susan Alpert Siegel, Ph.D. and Anne Carlson, Ph.D, wherein the Office action was discussed. Two abstracts, documenting a relationship between angiogenesis and periodontal disease, were forwarded to the U.S. Patent and Trademark Office for their consideration. For the Examiners' convenience, additional copies of these abstracts are attached hereto as Exhibits A and B. In addition, amendment of the independent claims was discussed.

**Election/Restriction**

The Office action states that the claims drawn to methods of inhibiting endothelial cell growth and inhibiting angiogenesis are pending. Thus, it is the Applicants' understanding that the Examiner has rejoined the subject matter of Groups I and II. Claims 2-4, 7-8, 61, 65 and 67 have been withdrawn from consideration, as being directed to a non-elected invention. It is the also the Applicants' understanding that the restriction requirement has been made final.

SAS/AC:gte 03/18/04 263459  
PATENTAttorney Reference Number 4239-58378  
Application Number 09/807,148**Information Disclosure Statement**

The Office action states that "the list of the Information Disclosure Statement" submitted on April 5, 2001 is missing from the file. Thus, it is the Applicants understanding that the PTO-1449 form has been misplaced. A copy of the PTO-1449 form submitted on April 5, 2001 is attached (Exhibit C).

Attached is a copy of the return post card documenting receipt by the United States Patent and Trademark Office (PTO) of the Information Disclosure Statement, the PTO-1449, and the cited references on April 5, 2001 (Exhibit D). Thus, it is the Applicants' understanding that no additional fee is due.

If the copies of the references are also missing from the U.S. PTO's file, then the Applicants respectfully request that the Examiner contact the undersigned by telephone, and additional copies of the references will be provided. If the references have already been received, or are otherwise available to the Examiner, Applicants respectfully request that the Examiner initial and date the attached PTO-1449 form to indicate that the references have been considered, and return a copy of the signed form to the Applicants' representative at the address listed below.

**Rejections Under 35 U.S.C. §112, first paragraph**

Claims 1, 5, 6, 13-17, 20-25, 57, 60, 62-64, 66, 68-70, 77-81 are rejected under 35 U.S.C. §112, first paragraph, as allegedly a genus of polypeptides that are defined only by sequence identity (90-98%) or as a fragment are not described in the specification. Claims 62 and 68 are canceled herein, rendering the rejection moot as applied to these claims. Applicants respectfully disagree with the rejection as applied to claims 1, 5, 6, 13-17, 20-25, 57, 60, 63-64, 66, 69-70, 77-81.

The specification clearly describes polypeptides with at least 95% identity to calreticulin (SEQ ID NO: 2). For example, these polypeptides are disclosed in the specification on page 12, line 8 to page 13, line 3. Specific computer programs are also disclosed that can be used for a comparison of sequence identity (see the specification on page 12, lines 20-25). In addition, a specific sequence of a polypeptide (SEQ ID NO: 3) with a 95% sequence identity to calreticulin is provided. This polypeptide inhibits endothelial cell growth (see the specification on page 32). Furthermore, the specification discloses that the first 120 amino acids are not essential for

SAS/AC:gtc 03/18/04 263459  
PATENTAttorney Reference Number 4239-58378  
Application Number 09/807,148

inhibiting endothelial cell growth (see the specification on page 11, lines 9-13, page 20, lines 25-30), indicating that these amino acids could be varied.

With regard to fragments of SEQ ID NO: 2 that inhibit endothelial cell growth or angiogenesis, the specification provides adequate written description for such fragments. Specifically, therapeutically effective fragments are described in the specification on page 11, lines 5-30. Moreover, the sequence of several active fragments (for example, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, and SEQ ID NO: 8) are disclosed. Indeed, the specification indicates that an amino acid sequence found between amino acids 132-180 of SEQ ID NO: 2 (also shown as SEQ ID NO: 6) is included in these fragments (see the specification at page 20, lines 10-25). As noted above, the specification discloses that the first 120 amino acids are not essential for endothelial cell growth (see the specification on page 11, lines 9-13, page 20, lines 25-30).

In order to clarify that the claimed polypeptides must be therapeutically effective, claim 1 has been amended to recite that the polypeptide "inhibits endothelial cell growth" and claim 5 has been amended to recite that the polypeptide "inhibits angiogenesis." Applicants note that assays for testing these activities are described in the specification on page 34, lines 30-38. Moreover, results from such testing of a polypeptide (SEQ ID NO: 3) having an amino acid sequence 95% identical to SEQ ID NO: 2, and results from testing of effective fragments of SEQ ID NO: 2 (SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, and SEQ ID NO: 8) are presented in the Examples section (see the specification on page 23, line 34 to page 25, Table 4 (angiogenesis), and on page 18, line 12 to page 22, Table 3 (endothelial cell growth).

Thus, Applicants submit that there is clearly sufficient descriptive support in the specification for polypeptides of at least 95% sequence identity to SEQ ID NO: 2, and therapeutically effective fragments thereof, that inhibit endothelial cell growth and/or inhibit angiogenesis. Reconsideration and withdrawal of the rejection is respectfully requested.

Claim 20 was rejected as allegedly not being enabled by the specification. The Office action asserts that the specification does not teach any relationship between angiogenesis and periodontal disease. Thus the Office action alleges that the specification is not enabling for claims directed to the use of a polypeptide with at least 95% sequence identity to SEQ ID NO: 2,

SAS/AC:gle 03/18/04 263459  
PATENTAttorney Reference Number 4239-58378  
Application Number 09/807,148

or a therapeutically effective fragment thereof, to treat periodontal disease. Applicants respectfully disagree with this rejection.

Applicants note that the specification at page 39, lines 11-13 teaches that angiogenesis is associated with periodontal disease. Moreover, Polverini *et al.* (*Crit. Rev. Oral Biol. Med.*, 6:230-247, 1995; Exhibit A) and Zoellner *et al.* (*J. Oral Pathol. Med.*, 18:333-338, 1989; Exhibit B) are two examples from the prior art that demonstrate it was known to those of skill in the art at the time the application was filed that a relationship existed between angiogenesis and periodontal disease.<sup>1</sup>

Legal precedent holds that the specification need not disclose what is well known in the art (*Lindemann Maschinenfabrik GmbH V. American Hoist & Derrick Co.*, 221 USPQ 481, 489 (Fed. Cir. 1984)). As the relationship between periodontal disease and angiogenesis was well known in the art at the time the application was filed, the mechanistic details of the relationship between angiogenesis and periodontal disease need not be fully described in the specification. Moreover, Applicants submit that a complete understanding of the mechanistic relationship between angiogenesis and periodontal disease is not necessary for one of skill in the art to practice the claimed methods. Reconsideration and withdrawal of the rejection is respectfully requested.

#### Rejection Under 35 U.S.C. §102

Claims 1, 5, 6, 57, 60, 62-64, 66, 68-70, and 78 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by U.S. Patent No. 5,426,097 (hereinafter the '097 patent; issued June 20, 1995). Claims 62 and 68 are canceled herein rendering the rejection moot as applied to these claims. Applicants respectfully disagree with this rejection as applied to claims 1, 5-6, 57, 60, 63-64, 66, 69-70 and 78, as amended.

The '097 patent teaches that calreticulin can be used to block or prevent thrombosis (blood clotting) in a subject in need of treatment with such an agent without causing a defect in hemostasis (the arrest of bleeding). A method for enhancing the action of other antithrombotic agents is further provided. These methods include intracoronary or intravenous administration of

<sup>1</sup> Copies of these references were faxed to the U.S. PTO on February 24, 2004. However, for the Examiner's convenience, additional copies are enclosed.

SAS/AC:gte 03/18/04 263459  
PATENTAttorney Reference Number 4239-58378  
Application Number 09/807,148

calreticulin at a dose of 0.04 mg/kg to 0.4 mg/kg (see the '097 patent at column 4 to column 5) into a subject to block or prevent the formation of a blood clot.

The Office action suggested that methods of inhibiting endothelial cell growth or angiogenesis in subjects are inherent to the methods disclosed in the '097 patent. Applicants respectfully disagree with this assertion.

Anticipation requires that each and every element of the claimed invention must be present in the prior art either explicitly or inherently (See *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1374 (Fed. Cir. 2001); *Mehl/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365, 52 USPQ2d 1303 (Fed. Cir. 1999)). Thus, if a claimed process is not disclosed in a single prior art reference, arguments of inherency are immaterial.

The '097 patent discloses that calreticulin can be administered to prevent blood clotting in a subject in need of antithrombotic therapy. Angiogenesis involves the development of new blood vessels (see Exhibit E), whereas thrombosis involves the development of clots within blood vessels (see Exhibit F). Since angiogenesis and thrombosis are two entirely different processes, a population of patients in need of antithrombotic therapy is clearly different from a population of patients in need of inhibition of endothelial cell growth, or in need of anti-angiogenic therapy. Thus, a *prima facie* case of anticipation has not been established for claims 1, 5-6, 57, 60, 63-64, 66, 69-70 and 78, as amended. Moreover, as these processes (thrombosis as compared to endothelial cell growth and angiogenesis) are so radically different, applicants submit that the '097 patent could not possibly be construed to render obvious claims 1, 5-6, 57, 60, 63-64, 66, 69-70 and 78, as amended.

Reconsideration and withdrawal of the rejection are respectfully requested.

#### **Obviousness-Type Double Patenting**

Claims 5, 22, and 23 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-9 of United States Patent No. 6,596,690. Applicants strongly disagree with this assertion.

However, solely in the interest of accelerating prosecution, submitted herewith is a terminal disclaimer that disclaims the terminal portion of any patent granted in this application that would extend beyond the expiration date of United States Patent No. 6,596,690.

SAS/AC:gte 03/18/04 263459  
PATENT

Attorney Reference Number 4239-58378  
Application Number 09/807,148

Applicants submit that the submission of this terminal disclaimer obviates the rejection.

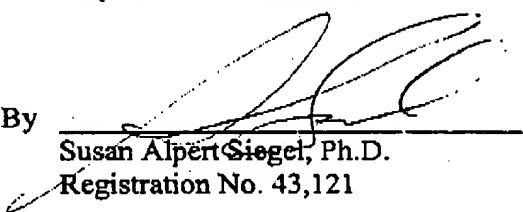
### Conclusion

Applicants submit that claims 1, 5, 6, 13-17, 20-25, 57, 60, 63-64, 66, 69-70, 77-81 are in condition for allowance, which action is requested. If any matters remain to be addressed before a Notice of Allowance is issued, the Applicants request that Examiner Yu contact the undersigned for a telephone conference at the telephone number listed below.

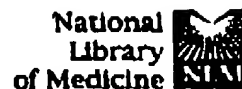
Respectfully submitted,

KLARQUIST SPARKMAN, LLP

By

  
Susan Alpert Siegel, Ph.D.  
Registration No. 43,121

One World Trade Center, Suite 1600  
121 S.W. Salmon Street  
Portland, Oregon 97204  
Telephone: (503) 226-7391  
Facsimile: (503) 228-9446



Entrez PubMed Nucleotide Protein Gene Structure OMIM PMC Journals Books  
 Search PubMed for Limits Preview/Index History Clipboard Details

About Entrez

Text Version

Entrez PubMed  
 Overview  
 Help | FAQ  
 Tutorial  
 New/Noteworthy  
 E-Utilities

PubMed Services  
 Journals Database  
 MeSH Database  
 Single Citation Matcher  
 Batch Citation Matcher  
 Clinical Queries  
 LinkOut  
 Caddy

Related Resources  
 Order Documents  
 NLM Gateway  
 TOXNET  
 Consumer Health  
 Clinical Alerts  
 ClinicalTrials.gov  
 PubMed Central

Privacy Policy

Abstract Show: 20 Sort Send to Text

1: Crit Rev Oral Biol Med. 1995;6(3):230-47.

Related Articles Links

## The pathophysiology of angiogenesis.

Polverini PJ.

Department of Oral Medicine, Pathology, and Surgery, University of Michigan School of Dentistry, Ann Arbor 48109-1078.

The formation of new capillary blood vessels, a process termed "angiogenesis", is one of the most pervasive and fundamentally essential biological processes encountered in mammalian organizations. Angiogenesis is an important event in a variety of physiological settings, such as embryonic development, chronic inflammation, and wound repair. It is a process that is tightly regulated in both time and space. Angiogenesis is driven by a cocktail of growth factors and pro-angiogenic cytokines and is tempered by an equally diverse group of inhibitors of neovascularization. Angiogenesis is also central to the etiology and pathogenesis of a number of pathological processes that include, among others, solid tumors, diseases of the eye, and chronic inflammatory disorders such as rheumatoid arthritis, psoriasis, and periodontitis. Based on recent work from several laboratories, it is now eminently clear that most if not all angiogenesis and vasoproliferative-dependent disease processes are not only a consequence of the unrestricted production of normal or aberrant forms of pro-angiogenic mediators but also the result of a relative deficiency in angiogenic-inhibitory molecules. In this review, I will describe how these multifunctional mediator systems function to coordinate and regulate the angiogenic response, and how disruption in the molecular controls that regulate the production of pro-angiogenic and angiostatic mediators leads to aberrant angiogenesis and disease. The implications of these findings in the development of novel therapeutic strategies for the treatment of diseases characterized by dysregulated angiogenesis will also be discussed.

### Publication Types:

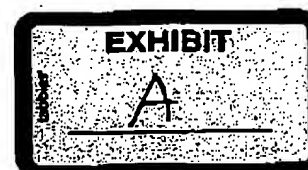
- Review
- Review, Tutorial

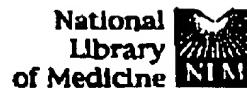
PMID: 8785263 [PubMed - indexed for MEDLINE]

Abstract Show: 20 Sort Send to Text

Write to the Help Desk  
 NCBI | NLM | NIH  
 Department of Health & Human Services  
 Freedom of Information Act | Disclaimer

Jan 29 2004 15:06:34





Entrez PubMed Nucleotide Protein Genome Structure OMIM PMC Journals Bi  
 Search PubMed for Limits Preview/Index History Clipboard Details

About Entrez

1: J Oral Pathol Med. 1989 Jul;18(6):333-8. Show: 20 Sort Text

Text Version

Entrez PubMed  
 Overview  
 Help | FAQ  
 Tutorial  
 New/Noteworthy  
 E-Utilities

PubMed Services  
 Journals Database  
 MeSH Database  
 Single Citation Matcher  
 Batch Citation Matcher  
 Clinical Queries  
 LinkOut  
 Cubby

Related Resources  
 Order Documents  
 NLM Gateway  
 TOXNET  
 Consumer Health  
 Clinical Alerts  
 ClinicalTrials.gov  
 PubMed Central

Privacy Policy

1: J Oral Pathol Med. 1989 Jul;18(6):333-8.

Related Articles, Links

### Perivascular hyaline deposits in inflamed gingival tissues.

Zoellner H, Hunter N.

Institute of Dental Research, United Dental Hospital, Surry Hills, NSW, Australia.

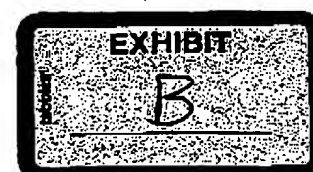
A perivascular hyaline material (PHyM) was found in gingival biopsies from patients with periodontitis, gingivitis and minimally inflamed gingiva. PHyM was found only in association with the sulcular or pocket epithelium. The extent and frequency of the deposits was quantitatively associated with inflammation of the gingival tissues, as well as with the apical region of periodontal pockets. Evidence for angiogenesis was found in association with the deposition of PHyM. The ultrastructure of the PHyM indicated that the material, which was of an amorphous hyaline appearance at the light microscope level, was composed of multiple basal lamina impregnated with irregular collagen fibrils, fine fibrils and cellular debris. The basal lamina material was degraded at many sites. Immunohistochemistry confirmed the abundance of type IV collagen, supporting the basal lamina origin for PHyM. It is proposed that the deposition of the hyaline matrix is related to the effect of angiogenic and injurious agents on the vascular endothelium. PHyM could contribute to the development of periodontitis by impairing the emigration of polymorphonuclear leukocytes into the gingival sulcus.

PMID: 2478697 [PubMed - indexed for MEDLINE]

1: J Oral Pathol Med. 1989 Jul;18(6):333-8. Show: 20 Sort Text

Write to the Help Desk  
 NCBI | NLM | NIH  
 Department of Health & Human Services  
 Freedom of Information Act | Disclaimer

Jan 29 2004 15:06:34





WDN/SAS:gtc 04/05/01 4239-58378 4375K.doc

EXPRESS MAIL LABEL NO. E1754020413US

DATE OF DEPOSIT: April 5, 2001

PATENT

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Tosato et al.

Application No.: To be assigned

Filed: Herewith

For: USE OF CALRETICULIN AND  
CALRETICULIN FRAGMENTS TO INHIBIT  
ENDOTHELIAL CELL GROWTH AND  
ANGIOGENESIS, AND SUPPRESS TUMOR  
GROWTH

Examiner: To be assigned

Date: April 5, 2001

Art Unit: To be assigned

CERTIFICATE OF EXPRESS MAILING

I hereby certify that this paper and the documents referred  
to as being attached or enclosed herewith are being  
deposited with the United States Postal Service on April 5,  
2001 as Express Mail Label No. EL754020413US in an  
envelope addressed to: BOX PCT, COMMISSIONER FOR  
PATENTS, WASHINGTON, D.C. 20231.



William D. Noonan, M.D.

Attorney for Applicant

INFORMATION DISCLOSURE STATEMENT PURSUANT TO 37 C.F.R. § 1.97(b)(3)

BOX PCT  
COMMISSIONER FOR PATENTS  
Washington, DC 20231


Sir:

Listed on the accompanying form PTO-1449 and enclosed herewith are several English-language documents. Applicants respectfully request that these documents be listed as references cited on the issued patent.

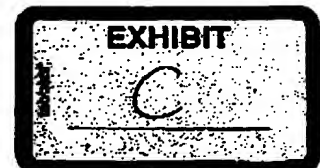
Applicants filed this Information Disclosure Statement before the mailing date of a first Office action on the merits. However, if the Patent Office determines that a fee is required for Applicants to file this Information Disclosure Statement, please charge any such fees, or credit overpayment, to Deposit Account No. 02-4550

Respectfully submitted,

KLARQUIST SPARKMAN CAMPBELL  
LEIGH & WHINSTON, LLP

By   
William D. Noonan, M.D.  
Registration No. 30,878

One World Trade Center, Suite 1600  
121 S.W. Salmon Street  
Portland, Oregon 97204  
Telephone: (503) 226-7391 / Facsimile: (503) 228-9446



WDN/SAS:glc 04/05/2001 4239-58378 4376

<b>INFORMATION DISCLOSURE STATEMENT</b>  <b>BY APPLICANT</b>	Docket: 4239-58378	App: To be assigned
	Applicant: Tosato et al.	
	Filed: Herewith	Art Unit: To be assigned

### U.S. PATENT DOCUMENTS

Init.*		Number	Date	Name	Class	Sub	Filed
		5,426,097	June 20, 1995	Stern et al.			
		5,591,716	Jan. 7, 1995	Siebert et al.			

### FOREIGN PATENT DOCUMENTS

		Number	Date	Country	Class	Sub	
		WO 95/13828	26 May 1995	PCT			
		WO 96/23001	1 Aug. 1996	PCT			
		WO 96/36643	21 Nov. 1996	PCT			
		WO 00/50080	31 Aug. 2000	PCT			
		2,140,814	24 July 1996	Canada			

### OTHER DOCUMENTS

			Dai et al., <i>Arteriosclerosis, Thrombosis and Vascular Biology</i> , 17(11):2359-2368, 1997 (abstract only); Medline abstract no. 1998073667, XP002133012
			Dedhar, <i>TIBS</i> , 19:269-271, 1994.
			Kishore et al., <i>Biochem. J.</i> , 322(2):543-550, 1997 (abstract only); Medline abstract no. 97218114, XP002133013
			Kuwabara et al., <i>J. Bio. Chem.</i> , 270(14):8179-8187, 1995.

EXAMINER:	DATE
*Examiner: Initial if considered, whether or not in conformance with MPEP 609; draw line through cite if not in conformance and not considered. Send copy.	

Information Disclosure Statement Page 1 of 2

WDN/SAS:pic 04/05/2001 4239-58378 437

<b>INFORMATION DISCLOSURE STATEMENT</b>  <b>BY APPLICANT</b>			Docket: 4239-58378	App: To be assigned
			Applicant: Tosato et al.	
			Filed: Herewith	Art Unit: To be assigned
			Kwon et al., <i>Mol. Biol. of the Cell</i> , 11:1433-1443, 2000.	
			McDonnell et al., <i>J. Bio. Chem.</i> , 271(14):7891-7894, 1996.	
			Michalak et al., <i>Biochem. J.</i> , 285:681-692, 1992.	
			Nash et al., <i>Mol. &amp; Cell. Biochem.</i> , 135:71-78, 1994.	
			Pike et al., <i>Chemical Abstracts</i> , 130(14), abstract no. 177891, 1999; & <i>J. Experimental Medicine</i> , 188(12):2349-2356, 1998.	
			Pike et al., <i>Blood</i> , 94(7):2461-2468, 1999.	
			Rokeach et al., <i>Protein Engineering</i> , 4(8):981-987, 1997.	
			Routsias et al., <i>Clinical and Experimental Immunology</i> , 91(3):437-441, 1993 (abstract only); Medline abstract no. 93185299, XP002133014.	
			Sontheimer et al., <i>J. Invest. Med.</i> , 43(4):362-370, 1995.	
			Stuart et al., <i>FEBS Letters</i> , 397:245-249, 1996.	

EXAMINER:	DATE
*Examiner: Initial if considered, whether or not in conformance with MPEP 609; draw line through cite if not in conformance and not considered. Send copy.	

Receipt is hereby acknowledged by the U.S. Patent Office, on the date stamped below, of a U.S. Patent Application under 35 U.S.C. § 371 for USE OF CALRETICULIN AND CALRETICULIN FRAGMENTS TO INHIBIT ENDOTHELIAL CELL GROWTH AND ANGIOGENESIS, AND SUPPRESS TUMOR GROWTH by Tosato et al.

Enclosed are the following:

09/807148

- ☒ Check in the amount of \$2,282.00 and cover sheet in duplicate
- ☒ Combined Declaration and Power of Attorney for Patent Application
- ☒ Preliminary Amendment
- ☒ Letter to the Official Draftsperson
- ☒ Preliminary Examination Report
- ☒ International Search Report
- ☒ Information Disclosure Statement
- ☒ Form PTO-1449 and copies of documents listed thereon.
- ☒ Deposit Acct. 02-4550 Authority

Express Mail No. EL754020413US, deposited April 5, 2001

Received:

4239-58378

WDN/SAS:gtc

JC04 Rec'd PCT/PTO 0 5 APR 2001

PREVIOUSLY DOCKETED



# Angiogenesis

From Wikipedia, the free encyclopedia.

**Angiogenesis** is the physiological process involving the formation of new blood vessels from pre-existing vessels. It is of clinical relevance, being a fundamental step in the transition of tumors from a dormant state to a malignant state.

Cancer cells are cells that have lost control of their ability to divide in a controlled fashion. A tumor consists of a population of rapidly dividing and growing cancer cells. Mutations rapidly accrue within the population. These mutations (variation) allow the cancer cells (or sub-populations of cancer cells within a tumor) to develop drug resistance and escape therapy. Tumors cannot grow beyond a certain size, generally 1-2 mm<sup>3</sup>, due to a lack of oxygen and other essential nutrients.

Tumors induce blood vessel growth (angiogenesis) by secreting various growth factors (e.g. Vascular Endothelial Growth Factor or VEGF). Growth factors, such as bFGF and VEGF can induce capillary growth into the tumor, supplying required nutrients and allowing for tumor expansion. Thus angiogenesis is a necessary and required step for transition from a small harmless cluster of cells, to a large tumor. Angiogenesis is also required for the spread of a tumor, or metastasis. Single cancer cells can break away from an established solid tumor, enter the blood vessel, and be carried to a distant site, where they can implant and begin the growth of a secondary tumor. Evidence now suggests that the blood vessel in a given solid tumor may be in fact be mosaic vessels, comprised of endothelial cells and tumor cells. This mosaicity allows for substantial shedding of tumor cells into the vasculature. The subsequent growth of such metastases will also require a supply of nutrients and oxygen.

Endothelial cells are much more genomically stable than cancer cells, and have a doubling time of approx 120 days. The genomic stability allied to their longevity (compared to the tumor cell), makes then an ideal target for therapies directed against them. They will not 'escape' therapy, as they will not undergo mitosis at such a rapid rate and carry any drug resistance variation through to the next generation within the lifespan of the therapy.

Angiogenesis research is a cutting edge field in cancer research, and recent evidence also suggests that traditional therapies, such as radiation therapy, may actually work in part by targetting the genomically stable endothelial cell compartment, rather than the genomically unstable tumor cell compartment. In short, the therapy is the selection agent which is being used to kill a cell compartment. Tumor cells evolve resistance rapidly due to rapid generation time (days) and genomic instability (variation), whereas endothelial cells are a good target because of a long generation time (months) and genomic stability (low variation).

This is a prime example of evolution in action at the cellular level, using a selection pressure to target and differentiate between varying populations of cells. The end result is the extinction of one species or population of cells (endothelial cells), followed by the collapse of the ecosystem (the tumor).

Angiogenesis-based tumour therapy relies on the existence of natural angiogenesis inhibitors like angiostatin, endostatin and tumstatin. These are proteins that mainly originate as specific fragments pre-existing structural proteins like collagen or plasminogen.

Retrieved from "<http://en.wikipedia.org/wiki/Angiogenesis>"

This page was last modified 15:14, 7 Mar 2004. All text is available under the terms of the GNU Free Documentation License (see Copyrights for details). Disclaimers. Wikipedia is powered by MediaWiki, an open source wiki engine.



# Thrombosis

From Wikipedia, the free encyclopedia.

**Thrombosis** is the formation of a clot or thrombus inside a blood vessel, obstructing the flow of blood.

## Table of contents

- 1 Causes
- 2 Types/classification
- 3 Embolisation
- 4 See also

## Causes

Classically, thrombosis is caused by abnormalities in one or more of the following (Virchow's triad):

- The composition of the blood
- Quality of the vessel wall
- Nature of the blood flow

The formation of a thrombus is usually caused by an injury to the vessel's wall, either by trauma or infection, and by the slowing or stagnation of blood flow past the point of injury. Occasionally, abnormalities in coagulation are to blame. Intravascular coagulation follows, forming a structureless mass of red blood cells, leukocytes, and fibrin.

## Types/classification

There are two distinct forms of thrombosis:

- venous thrombosis
- and arterial thrombosis

## Embolisation

If a bacterial infection is present at the site of thrombosis, the thrombus may break down, spreading particles of infected material throughout the circulatory system (pyemia, septic embolus) and setting up metastatic abscesses wherever they come to rest. Without an infection, the thrombus may become detached and enter circulation as an embolus, finally lodging in and completely obstructing a blood vessel (an infarction). The effects of an infarction depend on where it occurs.

Most thrombi, however, become organized into fibrous tissue, and the thrombosed vessel is gradually recanalized.

## See also

See also:



- pulmonary embolism
- myocardial infarct
- deep venous thrombosis
- renal vein thrombosis
- hepatic vein thrombosis (Budd-Chiari syndrome))

Retrieved from "<http://en.wikipedia.org/wiki/Thrombosis>"

This page was last modified 15:52, 3 Mar 2004. All text is available under the terms of the GNU Free Documentation License (see Copyrights for details). Disclaimers. Wikipedia is powered by MediaWiki, an open source wiki engine.